8EHQ-0596-13647

ORIGINAL

A

ICI Americas Inc.
286 Mantua Grove Road
West Deptford, NJ 08066-1732

May 2, 1995

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Office of Pollution Prevention and Toxics
US Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

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96 MAY -9 PM 2:48

Attn: TSCA 8(e) Coordinator

Re: Nonylphenol, CAS # 84852-15-3;
Nonylphenoxyacetic acid, CAS # 3115-49-9

ICI Americas Inc. was recently advised by our UK parent company, Imperial Chemical Industries plc, of positive findings for the above chemicals resulting from in vivo uterotrophic screening assays with rats. Nonylphenol (CAS # 84852-15-3) showed a statistically significant dose-related increase in uterine weight which appears to be consistent with an estrogenic activity. Nonylphenoxyacetic acid (CAS # 3115-49-9), a biodegradation product of ethoxylated nonylphenol showed a statistically significant increase in uterine weight at the top dose level only.

Octylphenol (CAS # 140-66-9) was also evaluated in the same assay at similar dose ranges as nonyl phenol but did not show a statistically significant increase in uterine weights. This observation is noteworthy in that octylphenol in earlier publically available in vitro studies showed potential estrogenic activity at lower doses, i.e., more activity than nonylphenol. This apparent reversal of activity levels was unexpected and may simply reflect the uncertainty in drawing conclusions with respect to risks to health or environment from these findings. Additional details including test protocols and statistical analyses of results are included in the enclosed report.

ICI Americas Inc. is submitting this information in accordance with our understanding of current EPA guidance for health/environmental effects under TSCA Section 8(e). In keeping with standard company practice, we are also reviewing our hazard communication literature and will evaluate appropriate work practices and implement changes as necessary.

Sincerely,

Joseph F. Jadlocki, Jr.
Manager, Regulatory Services

Contains No CBI

/8eNonyl.sam

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6/6/96

ZENECA CENTRAL TOXICOLOGY LABORATORY
ALDERELY PARK MACCLESFIELD
CHESHIRE UK

CATEGORY B REPORT (CONFIDENTIAL)
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Reports Centre

Sponsor:	ICI Surfactants
Sponsor Ref:	SU/95/12, SU/95/13 SU/95/14
CTL Ref:	Y00519/004 Y08976/001 Y08975/001
CTL Study No:	XR5126
Copy No:	

REPORT NO: CTL/R/1249

SCREENING OF CHEMICALS FOR EFFECTS ON UTERINE GROWTH IN IMMATURE FEMALE RATS: NONYL PHENOL, OCTYL PHENOL AND NONYLPHENOXYACETIC ACID

by

G J Moffat

THE DATA IN THIS REPORT HAVE NOT BEEN QUALITY ASSURED

Date of issue: 03 APR 1996

SCREENING OF CHEMICALS FOR EFFECTS ON UTERINE GROWTH IN IMMATURE FEMALE RATS: NONYL PHENOL, OCTYL PHENOL AND NONYLPHENOXYACETIC ACID

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the above study.

G J Moffat ..... Date 2ND APRIL 1996.

SCREENING OF CHEMICALS FOR EFFECTS ON UTERINE GROWTH IN IMMATURE FEMALE RATS: NONYL PHENOL, OCTYL PHENOL AND NONYLPHENOXYACETIC ACID

CONTENTS

CONTENTS (continued)

1. INTRODUCTION

A number of structurally diverse nonsteroidal substances, commonly used in modern industrial processes, have been shown to exhibit oestrogenic properties e.g the insecticide, chlordecone (Hammond et al., 1979). Concern has been raised about the potential hazard posed by the presence of these compounds within the environment.

Alkyl phenols and their derivatives are widely used as plastic additives and nonionic surfactants. Previous studies have indicated that this class of compounds can mimic oestrogen action in both *in vitro* e.g proliferation of the human mammary carcinoma cell line MCF7 (Soto et al., 1991) increased vitellogenin gene expression in rainbow trout hepatocytes (Jobling and Sumpter, 1993), and *in vivo* model systems e.g. induction of mitotic activity within rat endometrium (Soto et al., 1991).

Previous studies within CTL (XR4970 and XR4971) have examined the oestrogenic potential of two nonyl phenol derivatives - nonyl phenol (4) ethoxylate and nonyl phenol (9) ethoxylate. These studies evaluated the effects of these chemicals on uterine growth in immature female rats following oral administration, a standard *in vivo* mammalian test for oestrogenicity. Under the conditions of this assay, neither nonyl phenol (4) ethoxylate or nonyl phenol (9) ethoxylate produced any effect on uterine weight.

The studies presented here have employed the same *in vivo* model system to examine the oestrogenic potential of nonyl phenol, octyl phenol and nonylphenoxyacetic acid.

2. MATERIALS AND METHODS

2.1 Materials

Nonyl phenol, a pale yellow liquid [density = 0.95 (Merck Index, 10th edition, p6522); CTL reference number, Y00519/004], octyl phenol, a white solid (CTL reference number, Y08976/001) and nonylphenoxyacetic acid, a viscous brown liquid [density = 1.01-1.025 (Merck Index, 10th edition, p6522); CTL reference number, Y08975/001] were supplied by ICI Surfactants. Corn oil (CTL reference number, Y00790/004) was used as the dosing vehicle for all three compounds. The positive control compound, oestradiol benzoate, was supplied by Intervet UK Ltd., Cambridge, UK as an oily solution (5 mg/ml). Arachis oil was used as the dosing vehicle for oestradiol benzoate and was supplied by Sigma Chemical Company, Poole, Dorset.

All dosing solutions were prepared on the day dosing commenced and were stored at room temperature throughout the dosing period. These solutions were not analysed for achieved concentration of compound.

2.2 Animals

Immature female rats of the Alpk:APfSD (Wistar-derived) strain, supplied by BABU (Alderely Park, Cheshire, UK) were between 20-22 days old and in the weight range 37-48 g upon receipt. The animals were group housed at 6 per cage under standard conditions of temperature, humidity and light. PCD diet and mains water were provided *ad libitum*. The rats were allowed to acclimatise for 24 hours prior to dosing.

2.3 Experimental design

On arrival in CTL, the rats were weighed and sorted into three groups ie. rats weighing up to and including 40.9 g (Group A), rats weighing 41.0 - 44.9 g (Group B), and rats weighing more than 45.0 g (Group C). Animals in Group A were allocated one at a time to each of the 20 dose groups until all animals in Group A had been allocated. This process was repeated for Groups B and C. Each dose group was comprised of 6 animals in one cage.

For nonyl phenol, octyl phenol and nonylphenoxyacetic acid, the route of administration was by oral gavage at 10 ml/kg bodyweight. As a positive control, a group of animals received oestradiol benzoate (0.5 µg/animal, subcutaneously) dissolved in 0.1 ml arachis oil. Oestradiol benzoate was administered subcutaneously because it is rapidly inactivated when administered orally. Oestradiol benzoate is a well established inducer of uterine growth under the conditions used in this study (see CTL report CTL/R/1226). The corresponding control group received 0.1 ml arachis oil per animal.

A preliminary dose-finding study conducted within CTL (XR5124) established a maximum tolerated dose (MTD) in immature female rats for each of these three compounds - nonyl phenol (0.3 ml/kg ie. 285 mg/kg, based on a density of 0.95), octyl phenol (400 mg/kg) and nonylphenoxyacetic acid (0.4 ml/kg ie. 404 mg/kg, based on a density of 1.01). These MTDs were chosen as the highest dose levels used in this present study.

All animals received a single dose of the appropriate compound via the assigned route of administration on each day for three days. The animals were terminated 24 hours after the final dose.

2.4 Experimental Procedures

2.4.1 Bodyweights: The bodyweight of each animal was recorded upon delivery, immediately prior to dosing on each day and just prior to termination.

2.4.2 Clinical Observations: Prior to the start of the study, all rats were observed to ensure that they were physically normal and exhibited normal activity. Clinical observations were made on each animal at the time of weighing and dosing. The rats were also observed at least once daily (post-dosing) during the study.

2.4.3 Terminal Procedures: On the day of termination (ie. 24 hours after the third and final dose), the rats were terminated by an overdose of inhalation anaesthetic (Fluothane, supplied by Zeneca Pharmaceuticals). The uterus was removed from each animal, trimmed and blotted on filter paper to remove any fluid. The uterus was then weighed and discarded.

2.5 Statistical Analysis

Statistical comparisons between groups were carried out using Student's t-test. A level of significance of $p<0.05$ (two-tailed) was chosen. All values are expressed as group means ± SD (n=6 animals per group).

3. RESULTS

3.1 Oestradiol Benzoate

3.1.1 Bodyweight, Bodyweight Gain and Clinical Observations: There were no significant differences in the group mean terminal bodyweights or bodyweight gain between the oestradiol benzoate treatment group and the vehicle control group. Furthermore, there were no treatment related effects on clinical signs for the oestradiol benzoate treatment group.

3.1.2 Uterine Weight: Administration of oestradiol benzoate resulted in a significant increase in uterine weight. Using the group mean values, absolute uterine weight was increased 3.76-fold and the uterine:bodyweight ratio was increased 3.82-fold. These values are consistent with the known efficacy of oestradiol benzoate as a uterotrophic agent (CTL report number CTL/R/1226: using the group mean values, absolute uterine weight was increased 3.54-fold and the uterine:bodyweight ratio was increased 3.52-fold relative to the vehicle control group in this previous study).

3.2 Nonyl Phenol

3.2.1 Bodyweight, Bodyweight Gain and Clinical Observations: With the exception of the top dose group (285 mg/kg), in which bodyweight was significantly reduced to 83% of the vehicle control group, there were no significant differences in the group mean terminal bodyweights. However, the group mean bodyweight gains for the 95 mg/kg, 190 mg/kg and 285 mg/kg nonyl phenol dose groups were significantly reduced ie. 82%, 80% and 38% of the vehicle control group, respectively. Despite these reductions in bodyweight gain, no treatment related effects on clinical signs were observed for any of the nonyl phenol dose groups.

3.2.2 Uterine Weight: Immature female rats treated with nonyl phenol exhibited a statistically significant dose-related increase in uterine weight. At 47.5 mg/kg, 95 mg/kg, 190 mg/kg and 285 mg/kg, the absolute uterine weights were increased 1.29-, 1.41-, 1.60- and 1.81-fold repectively, relative to the vehicle control group. Furthermore, within the same dose groups, the uterine:bodyweight ratios were elevated 1.35-, 1.49, 1.73 and 2.20-fold respectively, relative to the vehicle control. No significant effect on uterine weight was observed at a nonyl phenol dose level of 9.5 mg/kg. These results clearly demonstrate that nonyl phenol can exert a significant uterotrophic effect in immature female rats at dose levels of 47.5 mg/kg or greater.

3.3 Octyl Phenol

3.3.1 Bodyweight, Bodyweight Gain and Clinical Observations: There were no significant differences in the group mean terminal bodyweights except for the two highest dose groups (300 mg/kg and 400 mg/kg) which were reduced to 90% and 77% of the vehicle control group, respectively. The group mean bodyweight gain was significantly reduced in the 300 mg/kg octyl phenol dose group ie. 63% relative to the vehicle control group, while the 400 mg/kg dose group exhibited no measurable bodyweight gain over the study period. However, there were no treatment related effects on clinical signs in any of the octyl phenol dose groups.

3.3.2 Uterine Weight: Under the conditions of this study, octyl phenol produced no significant effect on the absolute uterine weight in immature female rats. The relative uterine:bodyweight ratio was increased 1.18-fold in animals treated with octyl phenol at 100 mg/kg, 200 mg/kg and 300 mg/kg and was elevated 1.31-fold in animals receiving the top dose of octyl phenol (400 mg/kg). These small increases in relative uterine weight in the absence of any increase in absolute uterine weight are considered to be of no biological significance.

3.4 Nonylphenoxyacetic Acid

3.4.1 Bodyweight, Bodyweight Gain and Clinical Observations: . There were no significant effects on group mean terminal bodyweights over the study period. However, the group mean bodyweight gain was significantly reduced for the 202 mg/kg, 303 mg/kg and 404 mg/kg nonylphenoxyacetic acid dose groups ie. 79%, 56% and 63% relative to the vehicle control, respectively. There were no treatment related effects on clinical signs in any of the nonylphenoxyacetic acid dose groups.

3.4.2 Uterine Weight: At the top dose level (404 mg/kg), statistically significant increases in both absolute and relative uterine weight were observed (1.25- and 1.31-fold respectively) following treatment with nonylphenoxyacetic acid. However, at lower dose levels, nonylphenoxyacetic acid produced no significant effect on uterine weight.

4. CONCLUSIONS

Daily oral administration of nonyl phenol produced a significant dose related increase in uterine weight in immature female rats relative to the corn oil vehicle control group. The increase in absolute uterine weight ranged from 1.29-fold at 47.5 mg/kg to 1.82-fold at 285 mg/kg, which is considered to be the maximum tolerated dose for this experiment, while the uterine:bodyweight ratio increased from 1.35-fold at 47.5 mg/kg to 2.20-fold at 285 mg/kg.

Therefore, nonyl phenol, at a dose level of 9.5 mg/kg, produced no effect on uterine weight in this assay. However, at dose levels of 47.5 mg/kg or greater, nonyl phenol produced a uterotrophic response in immature female rats, which suggests that nonyl phenol possesses an intrinsic potential to mimic oestrogen action.

Octyl phenol, while producing no significant effect on absolute uterine weight, produced a statistically significant increase in relative uterine weight at four dose levels, 100 mg/kg (1.18-fold), 200 mg/kg (1.18-fold), 300 mg/kg (1.18-fold) and 400 mg/kg (1.31-fold). However, the biological importance of this slight response remains unclear. Therefore, these results indicate that octyl phenol does not possess the intrinsic potential to mimic oestrogen action, under the conditions of this study.

At the maximum tolerated dose (404 mg/kg), nonylphenoxyacetic acid produced a significant increase in both absolute (1.25-fold) and relative (1.31-fold) uterine weight. No significant effect on uterine weight was observed at lower dose levels.

As an internal standard, oestradiol benzoate (positive control) produced a uterotrophic effect of the expected magnitude in immature female rats.

5. REFERENCES

1 Hammond, B., Katzenellenbogen, B.S., Krauthammer, N. and McConnell, J. (1979) Estrogenic activity of the insecticide chlordecone (Kepone) and interaction with the uterine estrogen receptors. *Proc. Natl. Acad. Sci. USA* 76, 6641-6645

2 Soto, A.M., Justicia, H., Wray, J.W. and Sonnenschein, C. (1991) p-Nonyl phenol: an estrogenic xenobiotic released from "modified" polystyrene. *Environ. Health Perspect.* 92, 167-173

3 Jobling, S. and Sumpter, J.P. (1993) Detergent components in sewage effluent are weakly oestrogenic to fish: an *in vitro* study using rainbow trout hepatocytes. *Aquatic Toxicol.* 27, 361-372

SCREENING OF CHEMICALS FOR EFFECTS ON UTERINE GROWTH IN IMMATURE FEMALE RATS: NONYL PHENOL, OCTYL PHENOL AND NONYLPHENOXYACETIC ACID

TABLE 1

THE EFFECTS OF OESTRADIOL BENZOATE ON BODYWEIGHT AND UTERINE WEIGHT

Dose	Terminal bodyweight (g)	Bodyweight gain (g)	Absolute uterine weight (mg)	Relative uterine weight (% of bodyweight)
control	62.1 ± 3.7	14.4 ± 0.9	30.9 ± 5.3	0.050 ± 0.007
0.5 µg	61.1 ± 3.8	14.2 ± 1.3	116.1 ± 20.5***	0.191 ± 0.035***

Values shown are mean ± SD, n = 6 animals per group
*** statistically significant from arachis oil control, $p<0.001$

TABLE 2

THE EFFECTS OF NONYL PHENOL ON BODYWEIGHT AND UTERINE WEIGHT

Dose	Terminal bodyweight (g)	Bodyweight gain (g)	Absolute uterine weight (mg)	Relative uterine weight (% of bodyweight)
control	63.1 ± 3.2	13.7 ± 0.8	32.4 ± 7.1	0.051 ± 0.010
9.5 mg/kg	61.2 ± 3.9	13.4 ± 1.6	31.2 ± 5.0	0.051 ± 0.007
47.5 mg/kg	61.3 ± 3.8	13.5 ± 0.7	41.7 ± 1.9*	0.069 ± 0.007**
95 mg/kg	60.5 ± 3.3	11.3 ± 1.0***	45.6 ± 3.4**	0.076 ± 0.008***
190 mg/kg	59.3 ± 5.6	11.0 ± 1.8**	51.8 ± 3.0***	0.088 ± 0.008***
285 mg/kg	52.6 ± 5.0**	5.2 ± 3.7***	58.8 ± 3.6***	0.112 ± 0.008***

Values shown are mean ± SD, n = 6 animals per group
* statistically significant from corn oil control, $p<0.05$
** statistically significant from corn oil control, $p<0.01$
*** statistically significant from corn oil control, $p<0.001$

TABLE 3

THE EFFECTS OF OCTYL PHENOL ON BODYWEIGHT AND UTERINE WEIGHT

Dose	Terminal bodyweight (g)	Bodyweight gain (g)	Absolute uterine weight (mg)	Relative uterine weight (% of bodyweight)
control	60.9 ± 3.9	12.4 ± 1.1	27.3 ± 5.3	0.045 ± 0.007
10 mg/kg	60.8 ± 3.0	13.0 ± 0.8	27.6 ± 4.3	0.046 ± 0.008
100 mg/kg	61.9 ± 3.7	13.7 ± 1.1	32.7 ± 3.3	0.053 ± 0.004*
200 mg/kg	57.8 ± 4.4	10.8 ± 2.0	30.5 ± 3.3	0.053 ± 0.003*
300 mg/kg	55.1 ± 4.1*	7.8 ± 2.5**	28.8 ± 1.4	0.053 ± 0.005*
400 mg/kg	47.0 ± 3.4***	-0.2 ± 2.4***	27.8 ± 4.4	0.059 ± 0.008*

Values shown are mean ± SD, n = 6 animals per group
* statistically significant from corn oil control, $p<0.05$
** statistically significant from corn oil control, $p<0.01$
*** statistically significant from corn oil control, $p<0.001$

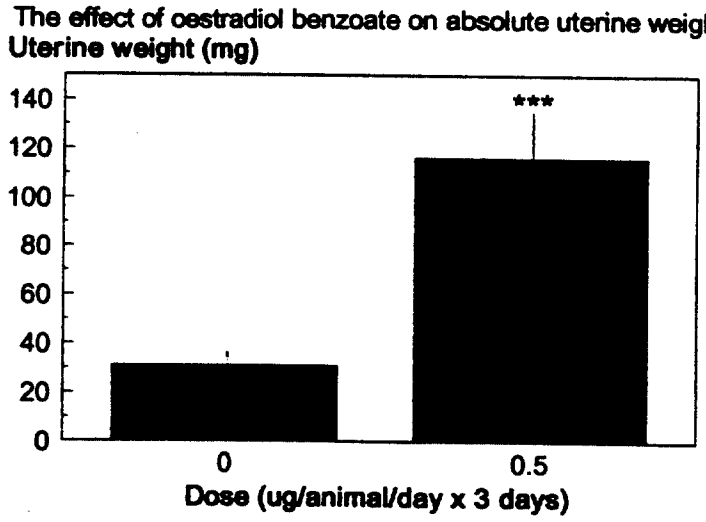
TABLE 4

THE EFFECTS OF NONYLPHENOXYACETIC ACID ON BODYWEIGHT AND UTERINE WEIGHT

Dose	Terminal bodyweight (g)	Bodyweight gain (g)	Absolute uterine weight (mg)	Relative uterine weight (% of bodyweight)
control	60.3 ± 2.8	13.1 ± 0.8	28.8 ± 4.6	0.048 ± 0.009
10.1 mg/kg	59.9 ± 2.6	11.9 ± 1.3	29.4 ± 2.0	0.049 ± 0.004
101 mg/kg	61.4 ± 4.2	11.2 ± 0.8	30.0 ± 2.7	0.049 ± 0.005
202 mg/kg	58.2 ± 3.2	10.4 ± 2.3*	29.4 ± 2.8	0.051 ± 0.006
303 mg/kg	56.7 ± 3.9	7.3 ± 3.8**	32.9 ± 6.9	0.058 ± 0.011
404 mg/kg	57.2 ± 4.3	8.3 ± 3.8*	35.9 ± 5.0*	0.063 ± 0.010*

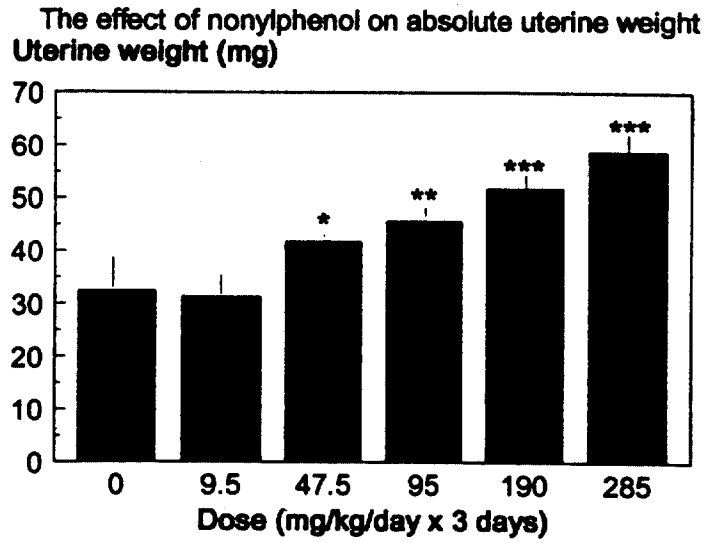
Values shown are mean ± SD, n = 6 animals per group
* statistically significant from corn oil control, $p<0.05$
** statistically significant from corn oil control, $p<0.01$

FIGURE 1



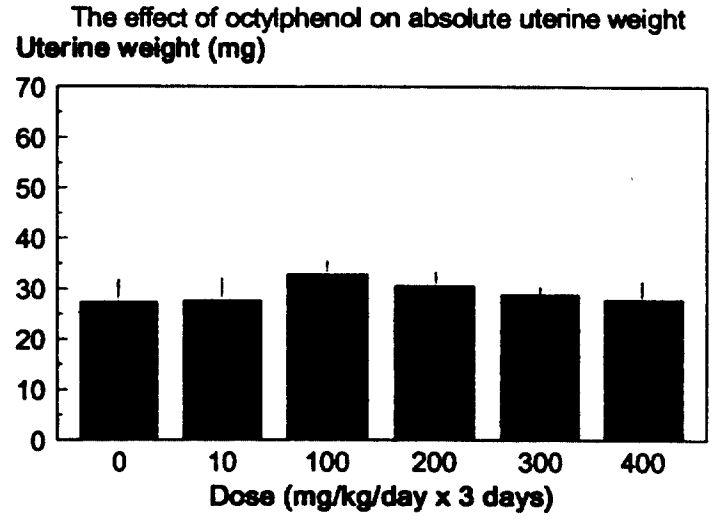
The complete data for oestradiol benzoate are shown in Table 1.
*** statistically significant from arachis oil control, $p<0.001$

FIGURE 2



The complete data for nonyl phenol are shown in Table 2.
* statistically significant from corn oil control, $p<0.05$
** statistically significant from corn oil control, $p<0.01$
*** statistically significant from corn oil control, $p<0.001$

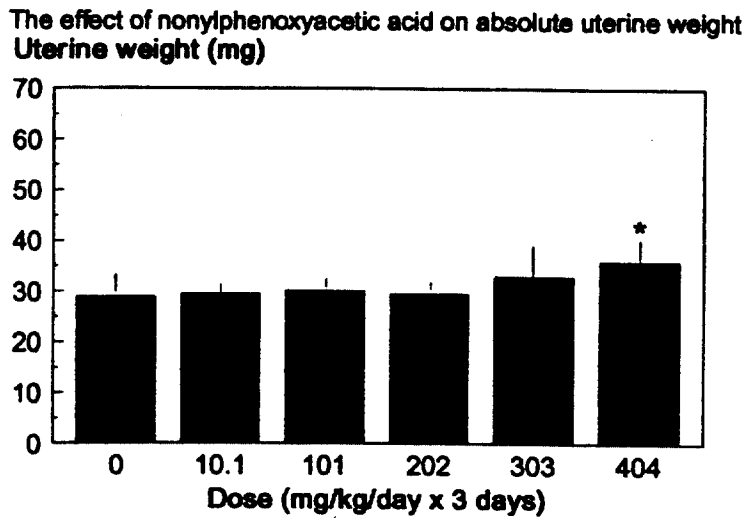
FIGURE 3



The complete data for octyl phenol are shown in Table 3.

SCREENING OF CHEMICALS FOR EFFECTS ON UTERINE GROWTH IN IMMATURE FEMALE RATS: NONYL PHENOL, OCTYL PHENOL AND NONYLPHENOXYACETIC ACID

FIGURE 4



The complete data for nonylphenoxyacetic acid are shown in Table 4.
* statistically significant from corn oil control, $p<0.05$

Triage of 8(e) Submissions

Date sent to triage: 7/17/96 (NON-CAP) CAP

Submission number: 13647A TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 -HERD (1 copy each)

STOX	CTOX	EPI	(RTOX)	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	NEUR

Other (FATE, EXPO, MET, etc.):_____

Notes:

☒ This is the **original** 8(e) submission; refile after triage evaluation.

☐ This **original** submission has been **split**; rejoin after triage evaluation.

☐ Other:

Photocopies Needed for Triage Evaluation

entire document: (0) 1 2 3

front section and CECATS: (0) 1 2 3

Initials: JW **Date:** 7/18/96

CECATS DATA:
Submission # 8EHQ- 0596 -13647 SEQ A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: ICI Americas Inc.

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 05/02/95 OTS DATE: 05/09/96 CSRAD DATE: 06/06/96

CHEMICAL NAME:	CAS#
	84852-15-3
	3115-49-9
	140-66-9

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	(0243)	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	(01) 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	(0248)	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	0224	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATA:

NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
(YES) (CONTINUE)	YES (DROP/REFER)	RAT	LOW	Plastic additives	
NO (DROP)	NO (CONTINUE)		MED	nonionic surfactants	
DETERMINE	REFER:		HIGH		

COMMENTS:

In vivo Uterotrophic Screening Assay
Oral gavage 20 groups of 6 animals
dose depends on cmpd (3 tested)
MTD = 285, 400, 404 mg/kg/day for nonyl phenol, octyl phenol, & nonylphenoxyacetic acid, respectively

(Med-High) NOAEL = 9.5 mg/kg/d ← LOAEL = 47.5 estrogenic activity
① Nonylphenol, ↓ body wt at 285
↓ group mean body wt beg. at 95–285.
No treatment related effects or clinical signs.
↑ uterine weight 47.5–285 mg/kg/day

(Low-Med) LOAEL = 300 for body wt ← No estrogenic activity
② Octylphenol, ↓ body wt at 300 & 400.
No effect on uterine wt

(Low-Med) LOAEL = 404 mg/kg/day for estrogenic action ←
③ nonylphenol acetic acid
↓ group mean body wt gain 202–404 mg/kg/d
↑ uterine wt at 404 mg/kg/day